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ORIGINAL ARTICLE

Collection and Transplantation of Peripheral Blood Stem Cells in Children: A Single-Center Experience

Çocuklarda Periferik Kan Kök Hücrelerin Toplanması ve Transplantasyonu: Tek Merkez Deneyimi

[1]Cengiz Zeybek, [2]Orhan Gürsel, [1]Ahmet Bolat, [3]İbrahim Eker, [4]Erman Ataş, [5]Ahmet Emin Kürekçi

[1]Department of Pediatrics, University of Health Sciences, Gülhane School of Medicine, Ankara, Türkiye
[2]Department of Pediatric Hematology, University of Health Sciences, Gülhane School of Medicine, Ankara, Türkiye
[3]Department of Pediatric Hematology and Oncology, University of Kocatepe, School of Medicine, Afyon, Türkiye
[4]Department of Pediatric Oncology, University of Health Sciences, Gülhane School of Medicine, Ankara, Türkiye
[5]Department of Pediatric Hematology, Lösante Hospital, Ankara,Türkiye

Correspondence

Cengiz Zeybek, Department of Pediatrics, University of Health Sciences, Gülhane School of Medicine, Ankara, Türkiye.

E-Mail: zeybekcengiz@yahoo.com

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ABSTRACT

Background/Aims: As a source of hematopoietic stem cells, peripheral blood stem cells have been used more frequently in both malignant and non-malignant diseases. There are some difficulties in the collection of peripheral blood stem cells (PBSC) from children compared to adults such as vascular access and extracorporeal circuit volume, especially in small children.
Methods: In this study, we present our experience in 63 children who underwent peripheral blood stem cell collection and transplantation between November 2016 and September 2023.
Results: The median age and weight of the children at the time of apheresis procedures were 10.25 years and 34 kg, respectively. Of 63 peripheral blood stem cell collection and transplantations, 48 were autologous and 15 were allogeneic. The median cell yield per apheresis procedure was 2.6 x 106 CD34+ cells/kg (0.6-9.66). Four of the total 63 patients and donors required multiple apheresis procedures. No significant side effects were observed after apheresis procedures.
Conclusion: We observed that in experienced hands, peripheral blood stem cell collection and transplantation in children is at least as safe and effective as in adults.

Keywords: bone marrow transplantation, hematopoietic stem cell transplantation, peripheral stem cell transplantation, children

ÖZ

Amaç: Hematopoetik kök hücre kaynağı olarak periferik kan kök hücreleri hem malign hem de non-malign hastalıklarda giderek daha çok kullanılmaktadır. Ancak çocuklarda özellikle de küçük çocuklarda erişkinlerden farklı olarak periferik kan kök hücre toplanmasında damar yolu ve ekstrakorporeal set volümü gibi zorluklarla karşılaşılabilmektedir.
Yöntem: Biz bu çalışmada Kasım 2016 ile Eylül 2023 tarihleri arasında, kendi merkezimizde periferik kan kök hücre toplaması ve transplantasyonu yaptığımız 63 çocuk hastayı sunuyoruz.
Bulgular: Aferez seansları sırasında çocukların ortalama yaş ve kiloları sırasıyla 10.25 ve 34 kg idi. Toplam 63 periferik kan kök hücre toplanması ve transplantasyonu işleminin 48'i otolog, 15'i allojeneik idi. Her aferez seansında elde edilen ortalama kök hücre sayısı 2.6 x 106 CD34+ hücre/kg (0.6-9.66) idi. Toplam 63 hasta ve donordan 4'üne multipl aferez seansları gerekti. Aferez seansları sonrası önemli bir yan etki gözlenmedi.
Sonuç: Deneyimli ellerde, çocuklarda periferik kan kök hücre toplaması ve transplantasyonunun en az erişkinler kadar güvenli ve etkili olduğunu gözlemledik.

Anahtar Kelimeler: kemik iliği nakli, hematopoetik kök hücre nakli, periferik kök hücre nakli, çocuklar

Introduction

Bone marrow transplantation (BMT), also known as hematopoietic stem cell transplantation (HSCT), currently uses bone marrow, peripheral blood, or umbilical cord as stem cell sources. BMT is used in hematological malignancies as well as hemoglobinopathies, immunodeficiencies, bone marrow failure, and inborn metabolic diseases (1). In recent years, the number of HSCTs using peripheral blood stem cell (PBSC) and cord blood has been increasing in children (2). Initial trials of PBSC transplantation had been performed mainly in adult patients, and there had been only a few reports in small children. However, over time, there has been an increasing trend in pediatric patients. Initially, the collection of PBSC in children was performed generally in younger cancer patients for autologous use, but in the course of time, beside autologous usage, more and more healthy children have been donating PBSC via apheresis for use by their ill siblings (3-5). There is a limited number of studies on the collection procedures, collection efficacy, and donor safety of PBSC in children. Here, we reviewed our records of 63 children who underwent apheresis procedures for PBSC collection out of 120 stem cell harvesting procedures performed in 115 children in our pediatric HSCT center.

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Complaints: geneltip@selcuk.edu.tr

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Material-Method

We retrospectively reviewed autologous and allogeneic PBSC collection procedures performed in our Pediatric Bone Marrow Transplant Unit between November 2016 and September 2023. All donors were medically evaluated before mobilization and collection. Written informed consent was obtained from the families of the donors before the procedures. The study was approved by the ethics committee of our hospital (2023/233).

PBSC mobilization was performed using granulocyte colony-stimulating factor (G-CSF) alone or in combination with plerixafor. G-CSF was administered as a single daily dose of 5 µg/kg for 5 consecutive days. Collection was performed on the 5th day. The targeted CD34+ cell count was determined as 2 x 106 CD34+ cells/kg. The additional doses of G-CSF were administered in cases that required a second or third dose of apheresis.

In all cases, PBSC collection was performed using a central venous catheter. The right jugular vein was preferred for central venous catheter applications. Access was obtained via a 7 French (for donors <20 kg) or 9 French (for donors ≥20 kg) central venous dialysis catheter (Medcomp, Harleysville, PA, US) with double lumens. Central venous catheter placement was performed under general anesthesia. In patients <25 kg, the extracorporeal line was primed with red blood cells to mitigate hemodynamic complications.

Mild sedation with hydroxyzine was administered to agitated patients during apheresis, and the blood pressure, oxygen saturation, and heart rate values of all donors were monitored throughout the apheresis procedure.

All collection procedures were performed using an AS.TEC204 (Fresenius NPBI, Dreieich, Germany) blood cell separator under manual control, via a P1Y disposable tubing set with an extracorporeal volume of 176 ml. A solution of 500 mL acid-citrate-dextrose (ACD-A) without heparin was infused at a whole blood to anticoagulant ratio of 1:15 for anticoagulation.

Results

The median age of the donors was 10.25 years (range: 3-18 years) and their median weight was 34 kg. The donor with the lowest weight of 14 kg was a 3-year-old child with stage IV neuroblastoma. The youngest donor was the same patient. The median body surface area of the donors was 1.16 m2 (range: 0.66-1.88). The median body mass index of the donors was 19.3 m2 (range: 12.2-25.4) (Table 1).

The indications and stem cell sources of our total 120 HSCTs in 115 children since 2016 are summarized in Table 2. Among these 120 HSCTs, 63 (52.5 %) were PBSC-derived. Most of the HSCTs which were PBSC-derived were performed with the diagnosis of solid malignancies (52 of 63 PBSC-derived transplantations, 82.5%). Among the 63 PBSC-derived transplants, 15 (24%) were allogeneic grafts from healthy siblings of patients under 18-year-old with parental consent, and 48 (76%) were autologous grafts (Table 3). One of the autologous graft cases was both PBSC and bone marrow-derived, and the procedure was performed for the diagnosis of acute myeloid leukemia. The characteristics of the donors who underwent apheresis procedures for PBSC collection are summarized in Table 1. Among the 63 PBSC-derived transplant cases, 51.,7% were boys, and 48.3% were girls.

Characteristics of the PBSC apheresis procedures, the pre-apheresis peripheral blood leukocyte counts of the donors, and their pre-apheresis polymorphonuclear leukocyte counts are given in Table 1. The median blood flow rate was 50 ml/min (range: 14-70). The median CD34+ cell yield was 2.6 x 106/kg (range: 0.6-9.66) after one apheresis procedure. The procedures had a median duration of 110 minutes. No significant adverse events related to apheresis were observed. Only 4 of the 63 patients (6.3%) required additional apheresis procedures. The characteristics of the donors who needed two or more mobilization procedures are summarized in Table 4 and 5. One of these cases was a 10-year-old girl diagnosed with neuroblastoma whose CD34+ hematopoietic stem cells count was 0.8 x 106/kg after purging in the first collection process. Her second collection process was performed after mobilization with G-CSF and plerixafor. Her CD34+ hematopoietic stem cells count was 5.3 x 106/kg after the second procedure.

Table 1. Characteristics of the donors who underwent apheresis procedures for PBSC collection and characteristics of PBSC apheresis procedures [a,b]

Parameters	Values
Donor characteristics	
Age (years)	10.25 (3-18)
Sex	
Male/Female	32 (51.7%)/31 (48.3%)
Weight (kg)	34 (14-77)
Height (cm)	137 (100-176)
BSA (m^2)	1.16 (0.6-1.88)
BMI (kg/m^2)	19.3 (12.2-25.4)
Leukocyte count ($x10^9/L$)	36 (20-60.2)
PMNL counts ($x10^9/L$)	30 (11.7-55)
Characteristics of PBSC apheresis procedures and products	
Blood volume of donors (ml)	2800 (1120-5600)
Volume of blood processed (ml)	7000 (2500-11250)
Apheresis time (min) Blood flow rate (ml/min)	110 (90-240) 50 (14-70)
Product volume (ml)	200 (110-890)
Product leukocyte count ($x10^9/L$)	150.4 (45-280)
CD34 (%)	0.29 (0.1-0.86)
CD34 ($10^6/kg$)	2.6 (0.6-9.66)

Data are presented as frequency (percentage) and median (min-max) values.

PBSC, peripheral blood stem cells; BSA, body surface area; BMI, body mass index; PMNL, polymorphonuclear leukocyte, CD, cluster of differentiation

a Total PBSC-derived HSCT count: 63

b Total PBSC apheresis procedure count:113

PBSC apheresis procedure count per HSCT: 1-4 times

Table 2. Indications and stem cell sources of HSCTs [a,b]

Parameters	Values				
Indications	Stem cell sources				Total
	PBSC	BM	PBSC+BM	BM+UCB	
Neuroblastoma [c]	21(17.50%)	3 (2.50%)			24 (20.00%)
Thalassemia major		13 (10.83%)		1 (0.83%)	14 (11.66%)
AML [c]	3 (2.50%)	9 (7.50%)	1 (0.83%)		13 (10.83%)
NHL	6 (5.00%)	7 (5.83%)			13 (10.83%)
ALL [c]	3 (2.50%)	9 (7.50%)			12 (10.00%)
HL [c]	12 (10.00%)				12 (10.00%)
FAA		4 (3.40%)			4 (3.40%)
LCH	2 (1.66%)	1 (0.83%)			3 (2.50%)
PNET	3 (2.50%)				3 (2.50%)
Ewing sarcoma	3 (2.50%)				3 (2.50%)
CML		3 (2.50%)			3 (2.50%)
MDS	1 (0.83%)	1 (0.83%)			2 (1.66%)
SCID	1 (0.83%)	1 (0.83%)			2 (1.66%)
JMML	1 (0.83%)	1 (0.83%)			2 (1.66%)
BPDCN [c]	1 (0.83%)	1 (0.83%)			2 (1.66%)
Osteopetrorickets	1 (0.83%)				1 (0.83%)
Germ cell tumor	1 (0.83%)				1 (0.83%)
Griscelli syndrome		1 (0.83%)			1 (0.83%)
Aplastic anemia		1 (0.83%)			1 (0.83%)
Wilm'erm cell tumor(FR (for donors Gürsel, Oğuzhan Babacan, Vural Kesik, Emin Kürekçis tumor	1 (0.83%)				1 (0.83%)
FAA+AML	1 (0.83%)				1 (0.83%)
WAS	1 (0.83%)				1 (0.83%)
AML+ALL	1 (0.83%)				1 (0.83%)
Total	63 (52.50%)	55 (45.88%)	1 (0.83%)	1 (0.83%)	120 (100%)

Data are presented as frequency (percentage) values.

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma; LCH, Langerhans cell histiocytosis; PNET, primitive neuroectodermal tumor; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; SCID, severe combined immunodeficiency; JMML, juvenile myelomonocytic leukemia; FAA, Fanconi aplastic anemia; WAS, Wiskott-Aldrich syndrome; BPDCN, blastic plasmacytoid dendritic cell neoplasm; BM, bone marrow; PBSC, peripheral blood hematopoietic stem cells; UCB, umbilical cord blood

[a] Total patient count:115

[b] Total hemopoietic stem cell transplantations:120

[c] One of the ALL patients underwent 2 allogeneic PBSC-derived HSCT procedures; One of the HL patients underwent 1 autologous PBSC-derived HSCT procedure, and 1 allogeneic PBSC-derived HSCT procedure; One of the neuroblastoma patients underwent 2 autologous PBSC-derived HSCT procedures; One of the AML patients underwent 2 allogeneic bone marrow-derived HSCT procedures; The BPDCN patient underwent 1 autologous PBSC-derived HSCT procedure and, 1 allogeneic bone marrow-derived HSCT procedure.

Table 3. Donor types of HSCTs

Parameters	Values				
	Stem cell sources				
Type of transplantation	PBSC	BM	PBSC+BM	BM+UCB	Total
Autologous [c]	48 (40.00%)	4 (3.33%)	1 (0.83%)		53 (44.17%)
Allogeneic [c]					67 (55.83%)
Full-matched	14 (11.67%)	50 (41.67%)		1 (0.83%)	65 (54.17%)
Well-matched	1 (0.83%)	1 (0.83%)			2 (1.67%)
Total	63 (52.50%)	55 (45.83%)	1 (0.83%)	1 (0.83%)	120 (100%)

Data are presented as frequency (percentage) values.

HSCT, hematopoietic stem cell transplantation; BM, bone marrow; PBSC, peripheral blood hematopoietic stem cells, UCB; umbilical cord blood

[a] Total patient count: 115

[b] Total hemopoietic stem cell transplantations: 120

[c] One of the ALL patients underwent 2 allogeneic PBSC-derived HSCT procedures; One of the HL patients underwent 1 autologous PBSC-derived HSCT procedure and, 1 allogeneic PBSC-derived HSCT procedure; One of the neuroblastoma patients underwent 2 autologous PBSC-derived HSCT procedure; One of the AML patients underwent 2 allogeneic bone marrow-derived HSCT procedure; The BPDCN patient underwent 1 autologous PBSC-derived HSCT procedure and, 1 allogeneic bone marrow-derived HSCT procedure.

Table 5. Characteristics of allogeneic donors who needed two or more mobilization procedures

Parameters First PBSC apheresis Second PBSC apheresis[a]					Hours after the start of PBSC apheresis CD34+ results as 10^6/kg of recipient weight			
Patient Sex (F/M)	Patient age (year)	Donor age (year) / Sex (F/M)	Diagnosis	Disease status	96 hours	144 hours	96 hours	P
M	15	17/M	AML	Relapse	4.4	3.47	2.78	9.04
M	17	16/F	ALL	Relapse	6.67	-	5.7	5.04

PBSC, peripheral blood hematopoietic stem cells; CD, cluster of differentiation; F, female; M, male; P, after purging; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia

a There was one month between the two PBSC apheresis procedures for the first patient; There were two months between the two PBSC apheresis procedures for the second patient.

Table 4. Characteristics of autologous donors who needed two or more mobilization procedures

Parameters First PBSC apheresis						Hours after the start of PBSC apheresis CD34+ results as 10^6/kg of recipient weight									
						Second PBSC apheresis[a]									
Sex (F/M)	Age (year)	Diagnosis	Disease status	Stage	CT cycles	72 hours	96 hours	120 hours	144 hours	P	PLX +/-	72 hours	96 hours	120 hours	P
F	10	NBL	Primary	IV	3-4 courses	0.4	1.4	-	-	0.8	+	-	-	9.7	5.3
M	14	NBL	Relapse	IV	6-course ICE + 3-course TCV	0.9	3.8	3.5	2	1.8	-	2.7	1.9	-	1.8

PBSC, peripheral blood hematopoietic stem cells; CD, cluster of differentiation; F, female; M, male; P, after purging; CT, chemotherapy; PLX, Plerixafor; NBL, neuroblastoma; TCV, Topotecan-cyclophosphamide-vincristine; ICE, ifosfamide carboplatin etoposide

a There was one month between the two PBSC apheresis procedures for the first patient; There were two months between the two PBSC apheresis procedures for the second patient.

Discussion

After 1968, bone marrow had been used for hematopoietic stem cell collection for a very long time. However, PBSC transplantation using G-CSF for stem cell mobilization began in the early 2000s, and the use of both autologous and allogeneic PBSC has gradually increased worldwide (6,7). According to data from the European Group for Blood and Marrow Transplantation registry (EBMT), pediatric recipients undergoing transplantations from any donor received bone marrow in 64% of the cases, PBSCs in 30% and umbilical cord blood in 6% of the cases (8, 9).

It has been reported that successful PBSC collection can be performed with G-CSF even in children weighing 10-15 kg without any significant complication (10). In fact, Nussbaumer et al. reported successful PBSC mobilization and collection procedures in 3 neuroblastoma patients under 10 kg (11). In this study, we showed that the mobilization and collection of PBSC in pediatric donors are a safe and effective procedures in expert hands. However, the priming of the extracorporeal separator line with red blood cells or albumin, as we did, has been recommended to ensure hemodynamic tolerance and a more effective collection process in such children.

The greatest advantage of PBSC transplantation over BMT is that neutrophil and platelet engraftment occurs in a shorter period of time, which results in fewer infection problems, shorter hospitalization periods and less need for transfusion (1). Perhaps, a disadvantage may be an increased risk of chronic graft-versus-host disease (12). This may be caused by the presence of mature T lymphocytes in the peripheral blood or the drugs used during the conditioning regime (13, 14). From a procedural point of view, potential advantages of PBSC collection include the absence of need for general anesthesia and post-BM harvest hospitalization, less physical difficulty, and less emotional stress. On the other hand, the collection procedure in children is more difficult than that in adults because of the low blood volume in the former, the high extracorporeal volume of disposable materials, the usage anticoagulants, particular problems related to the achievement of appropriate venous access, and side effects of the drugs used in mobilization (6, 15-18).

Normally, the amount of PBSC in the circulating blood is very low. However, this amount can be significantly increased by chemotherapy, applications of sequential growth factors applications such as G-CSF, and some signaling pathway inhibitors such as plerixafor (19, 20). We used G-CSF and plerixafor in our patients. For adequate CD34+ cell collection in PBSC transplantations, EBMT recommends the use of a single daily dose of 10 mg/kg of G-CSF (8). Nevertheless, we obtained sufficient stem cell counts in 59 of our 63 donors (93.6%) using G-CSF at a dose of 5 mg/kg/day. There are also different methods of using G-CSF in the literature (21). In recent years, the use of plerixafor has become increasingly common in patients who do not respond adequately to G-CSF treatment (22). The target stem cell count for the collection and infusion of PBSC in pediatric patients is a minimum of 2 x 106 CD34+ cells/kg (23). This level is 5 x 106 CD34+ cells/kg for adult patients (23, 24). In our patients, this level was adequate at an average of 2.6 x 106 CD34+ cells/kg. It has been demonstrated that younger age, more days of apheresis, and male gender are predictive of higher cell yields (16,19,20).

One of the most important issues when performing apheresis in children is that pediatric patients must have adequate hemoglobin and platelet counts. These levels have been reported as at least 12 g/dL hemoglobin and 40 x 109/L platelets for low-weight children (20,21,25,26).

The adverse effects of PBSC in donors are usually mild and minor. G-CSF-induced pain has been reported in less than 15% of pediatric donors (8,16,20). We observed headaches accompanied by low-grade fever and bone pain in 10% of patients after G-CSF use, and all of these symptoms were transient. If we had used G-CSF at higher doses such as 10 mg/kg/day, we might have encountered more side effects. Capillary leak syndrome, pericarditis, hypercalcemia, hypertension, hypotension and dyspnea accompanied by hypoxia, nausea and diarrhea, back pain and thrombocytopenia are other side effects reported in the literature in PBSC studies (1). These complications were reported to have been associated with the number of apheresis procedures (1). Depending on the condition of the patient or the underlying disease, the number of apheresis procedures usually varies between 1 and 3 (27). We performed multiple apheresis procedures in only 4 of our 63 patients.

The most commonly used anticoagulants during apheresis procedures are ACD-A or heparin. Some centers may use both simultaneously (28). The most important side effect of ACD-A use is citrate-induced hypocalcemia (28). We used ACD-A as an anticoagulant in our patients and did not encounter any side effects.

Study Limitations

The first limitation of our study was the limited number of patients. Secondly, we did not differentiate age and sex in terms of the PBSC counts after PBSC collection.

Conclusion

Although apheresis in children is technically similar to that performed in adults, some physicians are concerned about performing apheresis on children. However, previous studies and our study have shown that when this procedure is performed by an experienced team, it is safe, and sufficient counts of PBSC are obtained for autologous or allogeneic HSCTs.

Author Contributions

Conception: C.Z., O.G., İ.E., E.A., A.E.K, Data Collection and Processing: C.Z., A.B., O.G., İ.E., E.A., A.E.K., Design: O.G., İ.E., E.A., A.E.K., Supervision: O.G., E.A., Analysis

and Interpretation: C.Z., O.G., A.B., Literature Review: C.Z., Writer: C.Z., Critical Review: O.G.

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